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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/787,033	Applicant(s) Branden
	Examiner Dave Nguyen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 16, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *28-60* is/are pending in the application.

4a) Of the above, claim(s) *59 and 60* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *28-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1-27 have been canceled, claims 28-60 have been added by the amendment filed April 16, 2003.

Claims 28-60, to which the following grounds of rejection are applicable, are pending.

The species restriction is continued to carry over the newly added claims, drawn to a kit. As such, claims 59-60 are withdrawn from further consideration by the Examiner, as being drawn to a non-elected species.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-58, readable on a method of employing a transporting delivery complex to deliver a nucleic acid of interest across a biological membrane into a specific location within or on a cell, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a method of employing a PNA/FE conjugated to a nucleic acid/carrier to enhance the delivery of a nucleic acid into a cell. While the specification provides sufficient description of a method a method of using the conjugate or complex, wherein a PNA (which is defined as any DNA analogue comprising a pseudopeptide backbone consisting of aminoethyl glycine units, to which the nucleobases are attached via methylene carbonyl linkers, to deliver a nucleic acid across the cell membrane into the cytoplasm of a cell, and to deliver a nucleic acid across the cell membrane into the cytoplasm and nucleus of a cell, wherein an NLS is employed in the complex, the as-filed specification does not provide sufficient description of a genus of FE species and/or BE, and/or

an analogue or derivative other than the defined PNA, so as exhibit applicant's intended function of the complex, which is to deliver a nucleic acid to any specific location within or on a cell, *e.g.,* mitochondria, golgi apparatus, lysosome, a specific site of a target nucleic acid and/or protein complex present inside the cell, and/or any specific site within any of the organelles, chromosomes, nuclear membrane, nucleus or any target site located within or on a target cell. In addition, the newly added claims requires a conjugation of at least two or more FEs to the transporting complex, however, the claims embrace an invention that only one BE of PNA is required to be present. The as-filed specification, as evidenced by applicant's response, only teaches that two different PNA are required to carry a unique FE (functional element). As such, it is not apparent how a skilled artisan would have envisioned that applicant was in possession of the claimed invention wherein only one PNA is required to be present for complexing to at least two or more FE.

It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or materials and/or components containing unspecified structures of molecules that are essential for the making the methods as broadly claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of FE and/or BE and/or derivatives/analogues other than the defined PNA employed in the context of nucleic acid targeted delivery into or onto a cell.

Also, the claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming a complex composed of only one PNA/BE to complex with at least two or more FE within applicant's intended use, unspecified molecular structures of FE, BE, and/or a analogue or derivative of a PNA that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a

detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the FE and/or BE for use within the context of the claimed invention, which must exhibit the contemplated biological functions, *e.g.,* effecting an delivery of a nucleic acid to a specific location within or on a cell, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

An amendment of the claims as follows would obviate the rejection:

28. A synthetic transport complex for transferring a nucleic acid of interest across a biological membrane into a cell, wherein the complex is comprised of two or more functional elements (FE), each of which is complexed to a binding element (BE) in the form of a peptide nucleic acid (PNA), and a nucleic acid carrier, which comprises at least two BE target sequences and a nucleic acid of interest in a vector; said carrier being hybridized to said complex using the BE-BE interaction.

37. A method for transferring a nucleic acid of interest across a biological membrane of a target cell comprising administering to the cell the synthetic transport complex of claim 28.

45. The method of claim 37, wherein the biological membrane is a nuclear membrane, and wherein at least one functional element (FE) of said two or more functional elements (FE) is a protein, which enables both membrane translocation and nuclear transport of the nucleic acid of interest.

48. A kit comprising components for making a transport entity capable of transferring a nucleic acid of interest across a biological membrane into a cell, which kit comprises at least two binding elements (BEs) in the form of a peptide nucleic acid (PNA); two or more functional elements (FE); a plasmid containing said nucleic acid of interest; an oligonucleotide comprising a target for each of said BEs and being suitable for cloning in said plasmid, and optionally reagents suitable for such transfer.

Claims 28-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

28. A synthetic transport complex for transferring a nucleic acid of interest across a biological membrane into a cell, wherein the complex is comprised of two or more functional elements (FE), each of which is complexed to a binding element (BE) in the form of a peptide nucleic acid (PNA), and a nucleic acid carrier, which comprises at least two BE target sequences and a nucleic acid of interest in a vector; said carrier being hybridized to said complex using the BE-BE interaction.

37. A method for transferring a nucleic acid of interest across a biological membrane of a target cell comprising administering to the cell the synthetic transport complex of claim 28.

45. The method of claim 37, wherein the biological membrane is a nuclear membrane, and wherein at least one functional element (FE) of said two or more functional elements (FE) is a protein, which enables both membrane translocation and nuclear transport of the nucleic acid of interest.

48. A kit comprising components for making a transport entity capable of transferring a nucleic acid of interest across a biological membrane into a cell, which kit comprises at least two binding elements (BEs) in the form of a peptide nucleic acid (PNA); two or more functional elements (FE); a plasmid containing said nucleic acid of interest; an oligonucleotide comprising a

target for each of said BEs and being suitable for cloning in said plasmid, and optionally reagents suitable for such transfer.

The specification does not reasonably provide enablement for the presently pending claims encompassing any other claimed embodiment, specifically the embodiments embracing the delivery of a nucleic acid across or from any direction to a specific location within or on a cell, nor is the specification enabling for any targeted delivery of any specific location other than the nucleus of any target cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of the genus of FE, and/or BE, and/or PNA and/or derivatives thereof, which must exhibit the ability to specifically deliver a nucleic acid of interest to any specific location within or on a target cell, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended.

The claims also encompass a method of introducing a nucleic acid across cell membrane and yet to any specific location on a cell. While it is well-recognized in the prior art, *e.g.,* Verma *et al.* (Nature, Vol. 389, 18, September 1997), that a nucleic acid can be delivered across the cell membrane of a target cell intracellularly, it is not apparent as to how a nucleic acid can be delivered by a carrier such as a plasmid conjugated to a PNA/NLS to a specific

location on the surface of a target cell, particularly since the complex is required to go across either the cell membrane or a nuclear membrane of the target cell, and since the as-filed specification does not provide any guidance and/or evidence so as to demonstrate the claimed property within the context of applicant's claimed non-enabling embodiments.

In addition, the claims embrace a method of using of at least 2 FE to modular delivery of a nucleic acid to any specific location within a cell, *e.g.,* mitochondria, golgi complexes. However, the specification coupled with the knowledge in the art does not provide sufficient guidance as to how a skilled artisan uses the claimed method to modulate targeted delivery of any nucleic acid to any specific location within a target cell *in vitro* and/or *in vivo* so as to provide a beneficial effect, without undue experimentation, particularly on the basis of applicant's disclosure. While NLS are well-known in the art as a facilitator to enhance the delivery of a nucleic acid across the nuclear membrane into the nucleus of a target cell, there is no indicated specific guidance as to how any other FE can be employed to exhibit the claimed properties, *in vivo* delivery of a nucleic acid into any specific location of a target cell from any tissue. In order to practice the claimed invention , a skilled artisan would turn to the specification for guidance as to what is exactly the FEs so as to carry out the targeted delivery of any location within a target cell. However, the specification appears to disclose sufficient guidance only as to the use of a NLS as the FE to carry a nucleic acid across the nuclear membrane of a target cell. Next, there is no disclosure from the as-filed specification of any component of FE that is or is to be used to modulate the targeted delivery of a nucleic acid into any specific location other than the nucleus and/or cytoplasm of a target cell. Thus, the specification lacks sufficient guidance and/or description and/or factual evidence demonstrating as to how a skilled artisan practices the introduction of any nucleic acid to any specific location of any target cell *in vitro* and/or *in vivo* so as to produce a beneficial effect within the context of applicant's claimed invention, particularly on the basis of applicant's disclosure. The specification does not provide guidance and/or description of any and/or all other sited directing molecules to transfer the delivery of a substance inside in the cytosol of a target cell to any other specific cellular target location. Thus,

it is not apparent as to how one skilled in the art to determines, without undue experimentation, as to which of the other FE would exhibit the function as recited in the claim, particularly on the basis of applicant's disclosure.

Applicant's response with respect to the previous rejection which applicable to the previous claims which recites "direction thereof" has been noted, however, none of the presently pending claims recite such, and the rejection with respect to the issue of 'direction thereof" has been removed by the examiner. However, applicant's response is not found persuasive for other issues as set forth in the above stated rejectcion.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 48-51, 58 are rejected under 35 USC 102(e), as being anticipated by, or the alternative under 35 USC 103(a), as being unpatentable over Felgner (US Pat No. 6,165,720).

To the extent that the claims embrace:

A kit comprising components for making a transport entity capable of transferring a nucleic acid of interest across a biological membrane into a cell, which kit comprises one binding element (BE) in the form of a peptide nucleic acid (PNA); a cationic lipid as the first functional element, an NLS as the second functional element; a plasmid containing said nucleic acid of interest; an oligonucleotide comprising a target for said BE and being suitable for cloning in said plasmid, and optionally reagents suitable for such transfer.

Felgner is applicable as the prior art which teaches the same.

More specifically, Felgner teaches a kit comprising the following main components for making a nucleic acid delivery complex: a cationic lipid (column 4, lines 5-6) a PNA operably linked to a NLS such as SV40, which in turn is further operably linked to nucleic acid containing a PNA target to which the PNA hybridizes, *e.g.,* abstract, entire columns 3 and 4, particularly column 3 bridging column 4, column 7, columns 11 and 12. A modified PNA, which comprises a marker is also taught in column 3, lines 35-45. An embodiment wherein the linkers are disclosed so as to conjugate any of the essential components in the nucleic acid delivery composition is

also disclosed on column 12. Methods of using the transfecting reagents in the kit are disclosed in the working examples and the disclosure.

To the extent that the claims embrace a target cell comprising a cell wall or any other minor modifications which include the nature of spacers and/or linkers and/or NLS and/or suitable reagents such as buffers, it would have been obvious for one of ordinary skill in the art to have employed minor modification and/or as a matter of design choice to employed the kit comprising appropriate components including reagents to enhance the delivery and monitory of the distribution intracellularly in any cell of desire including those having a cell wall, particularly since the level of one ordinary skill in the art is relatively high, and since Felgner teaches that the complex when employed in any cell delivery method would enhance the entry of a desire nucleic acid into any target cell *in vitro* and/or *in vivo,* and would further facilitate the study and understanding of the cellular and molecular barriers to DNA delivery and the distribution of the delivered DNA intracellularly (columns 3-5, 10).

Thus, the claimed invention is anticipatory, or in the alternative, as a whole was *prima facie* obvious.

Applicant's response (pages 8, 9, 13, 14) has been considered by the examiner but is not found persuasive because of the following rejections, which are now specifically applicable to the newly added claims.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds* may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner

DAVE T NGUYEN
PRIMARY EXAMINER